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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,748	12/21/2001	Oluwole T. Aloba	2911.600	5061

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FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
HUI, SAN MING R	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,748	ALOBA ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-11, and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 2, 2004 has been entered.

The cancellation of claims 2-3 and 12-46 is acknowledged.

Claims 1, 4-11, and 47 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation "wherein the percent moisture of said dosage unit is less than 5%" is not supported by the originally filed specification or claims. Applicant is required to cancel the new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 2,156,599 ('599) or Stein, Stein is reference of record.

'599 teaches a pure powder of estradiol-3-acetate (See col. 1, Example 1).

Stein teaches a pure powder of estradiol-3-acetate (See col. 8, line 6-27, Example 3).

The estradiol-3-acetate powder taught in either '599 or Stein is considered a pure compound, which meets the limitations of the moisture contents recited in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein (US Patent 3,478,070), reference of record.

Stein teaches a unit dose composition containing estradiol 3-position derivatives including estradiol-3-acetate (See col. 2, lines 9-25; particular the compound of Formula I; also col. 8, lines 6-27, Example 3). Stein also teaches 1.25mg of estradiol-3-acetate as useful in treating menopausal syndrome (See col. 6, line 58-65). Stein also teaches the estradiol derivative composition may be formulated into oral dosage form such as tablets, or capsules (See col. 6, line 22). Stein also teaches various conventional carriers, such as suspending agents, and lubricants, can be incorporated into the composition (See col. 6, line 28-29).

Stein does not expressly teach the composition containing estradiol-3-acetate specifically.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate estradiol-3-acetate into the oral dose composition of Stein.

One of ordinary skill in the art would have been motivated to incorporate estradiol-3-acetate into the unit dose composition of Stein. It is known that estradiol 3-position derivatives can be formulated into oral unit dose composition such as tablet and capsule. Formulating any known estradiol 3-position derivatives, such as estradiol-3-acetate, into an oral dosage form such as tablet or capsule for the treatment of menopausal syndrome would have been reasonably expected to be useful.

Claims 6-9, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein (US Patent 3,478,070) as applied to claims 1, 4, 5, and 10-11 above, and

further in view of March (Advanced Organic Chemistry, 3rd ed., 1985, page 334-338), and Wolfe et al. (Journal of Lipid Research, 2000;41:368-375), references of record.

Stein suggests estradiol-3-acetate oral unit tablet or capsule composition.

Stein does not expressly teach the moisture content of the composition as less than or equal to 8%. Stein does not expressly teach the employment of an inhibitor of hydrolysis such as acetic acid. Stein does not expressly teach the additional medicament such as progestational agent is incorporated into the unit dose composition.

March teaches the process of acidic-catalyst hydrolysis of ester as completely reversible and symmetrical (See page 335, second paragraph). March also teaches that hydrolysis occurs only when the equilibrium is shifting to the right (See page 334).

Wolfe et al. teaches that the combination of estrogen and medroxyprogesterone is useful as hormonal replacement therapy, which has the benefits of reducing the VLDL and triglyceride levels (See page 374, col. 1, last paragraph to col. 2, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an inhibitor of hydrolysis such as acetic acid and a secondary agent, such as progestational agent to the composition of Stein. It would have been obvious to one of ordinary skill in the art at the time the invention was made to keep the moisture content as below 8%. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition through the process of granulation.

One of ordinary skill in the art would have been motivated to incorporate an inhibitor of hydrolysis such as acetic acid and a secondary agent, such as progestational agent to the composition of Stein. Since the products of 17β-estradiol-3-acetate hydrolysis are acetic acid and 17β-estradiol, adding acetic acid into the composition will help inhibiting the shifting of equilibrium to the right as taught in March. Therefore, incorporating acetic acid into the composition of Stein would have been considered as obvious to one of ordinary skill in the art since the addition of acetic acid would have been reasonably expected to inhibit or slow down the hydrolysis process. Optimizing the moisture content to be less than 8% would be considered obvious as being within the purview of skilled artisan, absent evidence to the contrary (See discussion below). Furthermore, based on Wolfe, it is known that the combination of estrogen and medroxyprogesterone, progestational agent, are useful in treating menopausal syndrome. Therefore, incorporating a progestational agent to an estradiol composition would have been reasonably expected to be useful in hormonal replacement therapy.

Response to Arguments

Applicant's arguments filed May 26, 2004 averring the cited prior art's failure to teach the herein claimed composition have been fully considered but they are not persuasive. The difference between the herein claimed composition and that of the cited prior art is the addition of acetic acid. As discussed above, the motivation to incorporated acetic acid into estradiol-3-acetate containing composition is that it is

reasonably expected acetic acid slowing down the hydrolysis process. Such hydrolysis process is well-known in the art as taught by March. Absent evidence to the contrary, possessing the teachings of the cited prior art, one of ordinary skill in the art would have been motivated to incorporate acetic acid into the estradiol acetate composition.

Applicant's arguments filed May 26, 2004 averring the cited prior art's failure to teach the motivation to keep moisture level to the herein claimed level have been considered, but are not found persuasive. Firstly, the claim recite 0-8% of water content or 0-5% of water content. The art clearly teaches estradiol-3-acetate as pure powders. Absent evidence to the contrary, it would be reasonably considered the moisture content is zero or close to zero percent since the art does not expressly teach the process of making the tablet involving water addition. Secondly, even *arguendo*, adjusting the moisture level would be seen to be within the purview of skilled artisan since moisture level would affect the degradation process of the active ingredients. Optimizing the moisture level is therefore, considered a routine practice in formulation pharmaceutical dosage forms.

Applicant's arguments filed May 26, 2004 with regard to Remington have been considered moot in view of the new ground of rejection.

Applicant's arguments filed May 26, 2004 averring March's failure to suggest the water content have been considered but are not found persuasive. March was cited to provide motivation to incorporate acetic acid into the estradiol-3-acetate composition. Applicant apparently mischaracterizes the references cited herein.

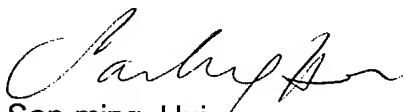
Applicant's arguments with regard to declaration by Dr. de Vries filed May 26, 2004 have been considered, but are not found persuasive. Applicant's statements in paragraph 5, page 2 of the declaration filed November 17, 2003 states "I do not believe that Stein et al. recognized the significant improvement in the relative bioavailability of estradiol found when 17β-estradiol-3-acetate is administered in oral preparation" are considered but are not found persuasive. Stein et al. clearly teaches the herein claimed compound, 17β-estradiol-3-acetate is useful as treatment for menopausal disorders when administered orally [emphasis added] (See col. 6, lines 58-65). Since Stein et al. teaches oral route of administration of the herein claimed compound, applicant's arguments are considered moot. Furthermore, the unexpected benefit demonstrated is to compare 17β-estradiol and the prodrug of 17β-estradiol (the ester, or acetate, of 17β-estradiol). It is not clear if it is a comparison to the closest prior art since the bioavailability of 17β-estradiol is not the basis of outstanding rejection set forth in the previous office action mailed July 15, 2003.

Applicant's rebuttal arguments filed May 26, 2004 averring superior stability have been considered, but are not found persuasive. Applicant argues that "Dr. de Vries' second declaration shows that solid dosage tablets of the present invention containing acetic acid show improved stability over similar tablets that did not contain acetic acid when stored under conditions likely to induce hydrolytic degradation". As discussed in the rejection set forth above, the reduction of rate of hydrolysis by acetic acid is expected. Therefore, unexpected slow down of degradation is not seen herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



San-ming Hui
Patent Examiner
Art Unit 1617